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Trial of Therapy with Monoclonal Antibody 17-1A in Pancreatic Carcinoma: Preliminary Results

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INTRODUCTION

Antibody CO17-1A is a murine monoclonal antibody of class IgG2a which was generated against a human colorectal carcinoma cell line, which binds to a variety of human gastrointestinal cancers, and which has been shown to inhibit the growth of various human gastrointestinal xenografts in athymic nude mice (1-3). Radioiodinated 17-1A has been administered to patients without complications for purposes of tumor imaging (4-5). In a pilot trial of immunotherapy with 17-1A in 20 patients with advanced gastrointestinal carcinomas no significant toxicity was observed, and circulating anti-mouse antibodies were detected in nine patients following injection (6). Three patients appeared to respond to 17-1A therapy, being free of detectable disease at followups ranging from ten to 22 months. One patient with carcinoma of the pancreas exhibited a clinical response. Developments of anti-idiotypic antibodies has been postulated to be involved in clinical response and disease remission in patients treated with 17-1A (7).

The present study was initiated to assess the clinical efficacy and toxicity of immunotherapy with monoclonal antibody 17-1A in advanced unresectable carcinoma of the pancreas. The preliminary experience with 25 patients is presented.

PATIENTS AND METHODS

Patients

Patients evaluated for 17-1A immunotherapy were referred to the National Institutes of Health with a diagnosis of adenocarcinoma of the pancreas which was metastatic or, if localized, which was considered surgically unresectable. For treatment, patients were required to have clinically evaluable disease, histologic confirma-

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tion of pancreatic carcinoma by National Cancer Institute pathologists, fully ambulatory performance status with a life expectancy of at least three months, and no history of previous immunotherapy. For patients referred after disease progression on previous radiotherapy or chemotherapy, a minimum of six weeks was required between previous treatment and the initiation of 17-1A immunotherapy. Informed consent was obtained from all patients, as approved by the clinical research institutional review board of the National Cancer Institute.

Clinical Evaluation

All patients evaluated for 17-1A therapy received a complete history and physical examination, blood count and coagulation profile, serum chemistry panel, chest x-ray with full-lung tomography, computerized axial tomographic (CAT) scanning of the abdomen, ultrasonographic scanning of the liver and pancreas, and bone scan. Other clinical evaluations, such as gastrointestinal contrast radiography or angiography, were performed as clinically required. Tumor sites were required to be visible and measurable on imaging studies for patient entry on study.

Antibody 17-1A

Monoclonal antibody CO17-1A was supplied by Centocor, Incorporated, of Malvern, Pennsylvania, under an investigational drug permit to the National Cancer Institute. 17-1A was harvested from the ascites of mice bearing intraperitoneal 17-1A hybridoma tumor, was purified by column chromotography, and was confirmed to be free of pathogens and pyrogens. The antibody was supplied in sterile vials, each containing 100 mg purified 17-1A.

Treatment Schedule

Patients were treated with an intravenous injection of antibody 17-1A alone or with antibody 17-1A absorbed to autologous peripheral blood mononuclear cells obtained by leukapheresis. Prior to immunotherapy, all patients received skin testing for hypersensitivity to 17-1A by intradermal injection of 1 mg 17-1A.

Antibody 17-1A Alone: The initial ten patients admitted to the study were treated with 400 mg 17-1A alone administered intravenously in 250 ml normal saline over approximately 30 minutes. The first patient treated received three 17-1A 400 mg doses, each dose separated by four weeks. The next nine patients received a single 17-1A 400 mg dose. Patients were hospitalized for observation for 24 hours following 17-1A infusion.

17-1A With Mononuclear Cells: Patients 11 through 25 admitted to the study were treated with 17-1A absorbed on autologous peripheral blood mononuclear leukocytes. Patients received leukapheresis for up to three hours on a centrifugal cell separator, and the mononuclear cell fraction was collected. In all patients, an attempt was made to collect in excess of 10^9 mononuclear cells. Following leukapheresis, 400 mg antibody 17-1A was incubated for 60 minutes with the collected mononuclear cell fraction, in a total volume 250 ml normal saline within the cell collection packet. After incubation, the entire contents of the cell collection packet were intravenously infused over approximately 30 minutes. Patients were hospitalized for observation for 24 hours following infusion.

Monitoring of Anti-Mouse and Anti-Idiotypic Response

After immunotherapy with 17-1A, serum samples were obtained weekly for six weeks to monitor for the appearance of anti-mouse immunoglobulin and for specific anti-idiotypic immune responses to 17-1A. Sera were stored at -70°C until assayed.

Assay for Anti-Mouse Immunoglobulin: An indirect immunoassay was utilized to assay patient sera for the presence of anti-mouse immunoglobulin, as described by Herlyn et al. (8), involving the detection by labeled anti-human antibodies of anti-mouse immunoglobulin in serum ehich was bound after incubation to 17-1A-coated beads.

Assay for Anti-Idiotypic Immunoglobulin: An inhibition radioimmunoassay was utilized to detect anti-idiotypic antibodies to 17-1A in the sera of treated patients, as described by Herlyn et al. (8), utilizing the inhibition of binding of labeled anti-idiotypic antiserum to monoclonal antibody 17-1A by human anti-idiotype present in serum.

Monitoring for Clinical Response to 17-1A Treatment

Following treatment with 17-1A, all patients were followed clinically at six-week intervals to assess clinical response. Patients routinely received blood count, serum chemistry profile, chest x-ray, and abdominal ultrasonography with computerized axial tomography. Other diagnostic tests were performed as clinically indicated. Patients were followed until objective disease progression or death, or until a patient requested to withdraw from the study. While on study, no patient received treatment for pancreatic carcinoma other than 17-1A immunotherapy.

Criteria for Response to Treatment

Response to 17-1A treatment was based upon objective measurements of tumor sizes obtained on imaging studies, comparing post-treatment followup measurements with pre-treatment values. Criteria for response were defined as: Complete response -- no evidence of malignancy; partial response -- reduction in size (product of perpendicular diameters of lesion) of measurable lesion by $\geq$50% in combination with a lack of enlargement in all lesions and a lack of appearance of new lesions; progressive disease -- increase in size (product of perpendicular diameters) of any measurable lesion by >50%, or the appearance of any new lesion, or patient death related to disease; stable disease -- failure to meet criteria for complete or partial response or for progression, <50% change in size of any measurable lesion in combination with a lack of appearance of new lesions.

Analysis of Treatment Effects

Patients were observed clinically after 17-1A therapy for toxicity and clinical response. Time to disease progression, survival, and response rates were recorded. The development of anti-mouse and anti-idiotypic circulating antibodies was recorded. Comparisons of survivals and times to disease progression among patient groups (responders or non-responders, 17-1A alone or 17-1A with mononuclear cells, postive or negative anti-idiotypic response) were performed using the generalized Wilcoxon life-table method. Comparisons of incidences of responses were made using chi-square analysis.

RESULTS

Number of Patients Treated

Twenty-five patients received monoclonal antibody C017-1A (Table 1). Ten patients received 17-1A alone, nine receiving a single 400 mg dose and one receiving three separate 400 mg doses. Fifteen patients received a single 400 mg dose 17-1A absorbed to autologous peripheral blood mononuclear cells, ranging in cell number from 0.8×10^9 to 19.0×10^9 cells per treatment.

Toxicity

No toxicity was observed which was attributable to treatment with antibody 17-1A, either 17-1A infusion alone or 17-1A absorbed on autologous peripheral blood mononuclear cells. No patients demonstrated hypersensitivity on skin testing with 17-1A.

One patient developed peritonitis and eventual fatal sepsis one week following infusion of 400 mg 17-1A. Clinical and autopsy findings showed the sepsis arose from the perforation of a surgical biliary bypass (cholecystojejunostomy) performed prior to referral for 17-1A therapy. It was felt unlikely that 17-1A

TABLE 1. PATIENTS TREATED WITH MONOCLONAL ANTIBODY 17-1A

17-1A ALONE:

10 patients (6M-4F)
age range 53-75 (median 63)
5 prior antineoplastic therapy, 5 no prior therapy
3 localized disease, 3 disseminated disease
8 primary disease, 2 recurrent after resection
10 evaluable for response, 0 pending, 1 withdrawal

17-1A + MONONUCLEAR CELLS:

15 patients (7M-8F)
age range 33-64 (median 51)
3 prior antineoplastic therapy, 12 no prior therapy
9 localized disease, 6 disseminated disease
15 primary disease, 0 recurrent after resection
9 evaluable for response, 6 pending, 1 withdrawal

therapy contributed to the septic complication. No other patients developed any complications within three weeks of 17-1A treatment.

Anti-Mouse and Anti-Idiotypic Response

Among the 25 patients treated with 17-1A, 23 developed circulating antibodies to mouse immunoglobulin within three weeks of immunotherapy. Anti-mouse immunoglobulin was detected in nine of the ten patients treated with 17-1A alone and in 14 of the 15 patients treated with 17-1A and mononuclear cells.

Anti-idiotypic circulating antibodies were detected within three weeks of 17-1A treatment in 11 of 25 patients. Anti-idiotype was present in three of ten patients treated with 17-1A alone and in eight of 15 patients treated with 17-1A and mononuclear cells.

Clinical Response to Treatment

Nineteen patients have been followed sufficiently after 17-1A treatment to determine clinical response; six patients have been followed with stable disease, insufficient to classify as response or progression, and are considered as pending in status.

Four patients exhibited objective partial responses (Table 2). Three partial responses ocurred in the patient group receiving 17-1A alone, one response occurred in the group receiving 17-1A and mononuclear cells. Two responses occurred in primary pancreatic masses, and two responses occurred in hepatic metastatic deposits. Three responses were clinically evident by six weeks following therapy; one was evident by 12 weeks. Two responses persisted for six weeks, one response continues to persist at 13 weeks, and one response continues to persist at 40 weeks (although the patient voluntarily withdrew from study at 18 weeks and received a single cycle of trimetrexate chemotherapy shortly following withdrawal). No complete responses were observed. At the time of analysis, median time to disease progression for all responders was 12 weeks.

Fifteen patients exhibited progressive disease after 17-1A treatment, seven in the group receiving antibody 17-1A alone and eight in the group receiving 17-1A and mononuclear cells. Progressive disease developed in the primary pancreatic mass in two patients, in the liver in seven patients, and in various other sites in seven patients. Median time to disease progression for all non-responders was six weeks, significantly shorter than the 12-week median time to progression for all responders (p=0.02).

TABLE 2. CLINICAL RESPONSES TO 17-1A TREATMENT

Patient	Stage Disease at Time 17-1A Rx	Prior Rx	Evaluable Disease Sites	Sites Response	Duration Response	Anti-Mouse	Anti-Idiotype	Survival or F/U Status
C	dissemi-nated	radia-tion chemo	pancreas liver	liver	6 wks	2+	-	dead 12 wks
D	local	none	pancreas	pancreas	40 wks	+	2+	alive 40 wks (with-draw at 18 wks 1 cyle chemo)
I	dissemi-nated	chemo	pancreas liver	pancreas	6 wks	2+	-	dead 14 wks
V	dissemi-nated	none	pancreas liver	liver	16 wks	2+	-	alive 16 wks

Among the 11 patients mounting an anti-idiotypic response to 17-1A, only one patient exhibited a clinical response. The patient developing anti-idiotypic antibodies showed only a low level of anti-idiotype response and a response of short duration. Three clinical responses were observed among the 14 patients failing to develop anti-idiotypic antibodies. All four clinical responses were included among the group of 23 patients producing anti-mouse immunoglobulin.

Survival

Median survival for all patients on study was 12 weeks at the time of analysis. Median survival for the four patients exhibiting clinical responses was 14 weeks, similar ($p=0.20$) to the survival of the 15 patients exhibiting no clinical response and to the survival of the six patients currently being followed for possible responses (Figure 1). Survival durations were similar at the time of current analysis ($p=0.35$) in the patient group developing anti-diotypic antibodies as compared to the group failing to develop an anti-idiotype response (Figure 2).

DISCUSSION

Monoclonal antibody CO17-1A has been shown to react with a variety of human gastrointestinal carcinomas, to inhibit the growth of tumor xenografts, and to localize to solid tumors in hosts bearing neoplasms (1-7). Considerable interest in antibody 17-1A as a possible therapeutic agent was generated by the demonstration that 17-1A was tolerated with acceptable toxicity when administered to patients and by the assertion that regressions of advanced tumors, including carcinoma of the pancreas, were observed following systemic administration of 17-1A (6). The present study was initiated to attempt to demonstrate any clinical activity of 17-1A in advanced unresectable adenocarcinoma of the pancreas.

Twenty-five patients were treated with antibody 17-1A, with 19 evaluable for clinical response at time of current analysis. No toxicity attributable to 17-1A was observed. Development of anti-murine immunoglobulin was detectable in 92% of patients within three weeks of treatment with 17-1A, although anti-idiotypic antibody was measurable in only 44%.

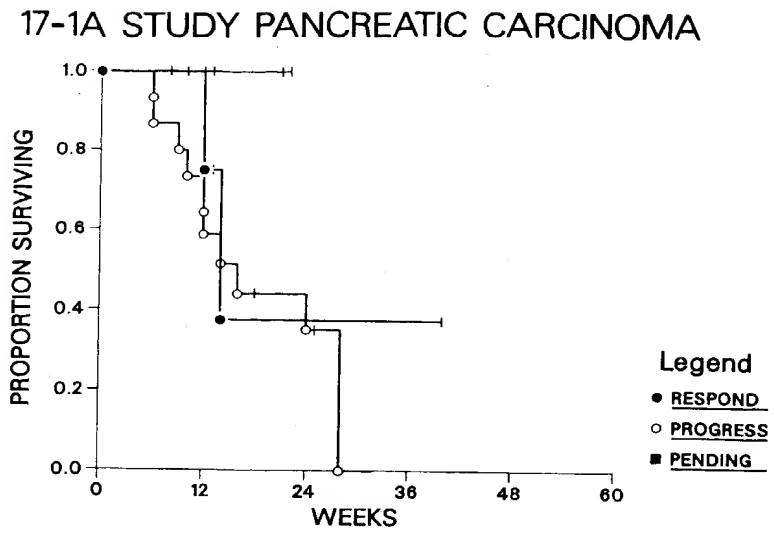

FIG. 1. Survival of patients receiving therapy with antibody 17-1A, including four patients demonstrating clinical partial responses (respond), 15 demonstrating no response (progress), and six followed without clinical response or progression at the time of analysis (pending).

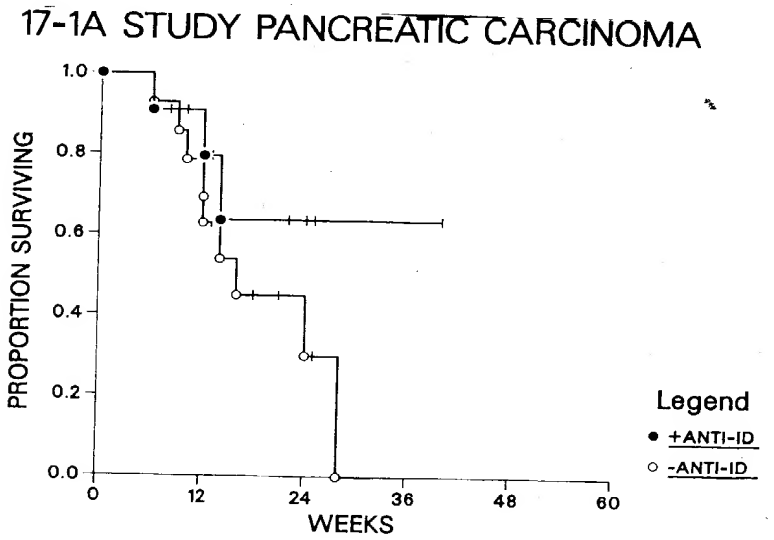

FIG. 2. Survival of patients receiving therapy with antibody 17-1A, including 11 patients developing anti-idiotypic antibodies (+anti-id) and 14 failing to develop anti-idiotypic antibodies (-anti-id).

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Objective clinical responses were observed in 21% of treated patients. Responses were all partial and generally of limited duration. Response rates did not statistically differ (p=0.34) between patients treated with antibody 17-1A alone (3/10 evaluable patients) or treated with 17-1A and mononuclear cells (1/9 evaluable). Clinical responses did not correlate (p=0.61) with the presence of anti-idiotypic antibody (1/7 evaluable patients) or with the absence of circulating anti-idiotype (3/12 evaluable). Although time to disease progression was significantly longer when clinical responders were compared to non-responders (p=0.02), no significant differences in survival (p=0.56) were observed at the time of analysis between patients in whom objective disease responses were observed and patients in whom no reduction of tumor burden was detected.

The study at the time of current analysis suggests that immunotherapy utilizing monoclonal antibody C017-1A can result in objective regression in some patients with carcinoma of the pancreas. The mechanism of action is unknown, but may involve direct effects on the neoplastic cells by the antibody or may involve mechanisms which stimulate endogenous immune reactions. The development of anti-idiotypic antibodies has been postulated to be involved in certain instances of tumor regression following monoclonal antibody therapy (7). However, a lack of correlation between the development of anti-idiotype and clinical response was observed in the present investigation. It is possible that anti-idiotype is not a major immunologic mediator of response. It is also possible that the detection of anti-idiotype failed to correlate with clinical responses because anti-idiotypic responses may have been missed if serum samples were drawn before or after but not during the response. Antibodies produced in the host against the anti-idiotype might play a role in clinical response and would not be detected in assays for anti-idiotype.

The present study requires further followup of treated patients to assess overall reponse rate. Further investigations of varying doses of antibody, the role of autologous peripheral blood monocytes, and anti-idiotypic responses are necessary to define the place of antibody 17-1A in the treatment of pancreatic cancer and to speculate on mechanisms of action involved in clinical responses.

ABSTRACT

Monoclonal antibody 17-1A was administered to 25 patients with advanced unresectable carcinoma of the pancreas. Ten patients received 17-1A alone in 400 mg doses delivered intravenously, while 15 patients received 400 mg 17-1A absorbed on to autologous peripheral blood mononuclear cells collected by leukapheresis (usual yield $>10^9$ cells). No toxicity was observed. Twenty-three patients developed circulating anti-murine immunoglobulin within three weeks of treatment, and 11 patients developed circulating anti-idiotypic immunoglobulin. Four out of 19 clinically evaluable patients (21%) showed objective regressions of tumor. Response did not correlate with the presence or absence of anti-idiotypic antibody and did not correlate with the method of treatment with 17-1A alone or 17-1A and mononuclear cells, at the time of current analysis.

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